CHROMOSOMAL TRANSLOCATIONS: DANGEROUS LIAISONS, Janet D. Rowley, Departments of Medicine and of Molecular Genetics and Cell Biology, University of Chicago, Chicago, Illinois.

Recurring chromosome translocations have been most closely associated with human leukemias and lymphomas. Recently, they have been shown to occur in sarcomas as well. In each type of tumor, the translocations are relatively specifically associated with particular subtypes of these tumors. Chromosome translocations have one of two general consequences. Those found in many lymphoid leukemias and lymphomas involve the juxtaposition of an antigen receptor gene (either one of the immunoglobulin genes in B lineage or T cell receptor genes in T lineage tumors) and a proto-oncogene leading to the aberrant expression of the normal protein produced by the proto-oncogene. In contrast, most of the translocations in myeloid leukemias and in sarcomas result in a fusion of the two genes at the translocation breakpoints and thus they give rise to a new fusion or chimeric gene, mRNA and protein.

Cloning the translocation junctions has identified the genes affected by the breakpoints in these malignant diseases. Well over three dozen new genes have been identified in this process. Some of these genes are not normally active in hematopoietic cells. Although the genes that are involved participate in a number of steps in the complex pathway of transmitting growth regulatory signals from the cell surface to the nucleus, most of those identified in the acute leukemias and lymphomas act as transcriptional activators. That is they are DNA binding proteins that directly regulate the level of transcription of the target genes. All types of DNA binding motifs are involved including zinc fingers, leucine zippers, homeobox domains, LIM domains and helix-loop-helix domains. Some of the genes recently cloned from breakpoint junctions in sarcomas, also act to regulate transcription. Although the genes involved in leukemia and lymphoma generally differ from those in sarcomas, there are a few exceptions.

Part of the challenge for the future is to understand the mechanisms leading to recurring translocations and also to understand the tumor-specificity of the translocations. It is hoped that this increasing understanding of the biology of these malignant diseases will lead to more accurate diagnosis, to improved therapy, and possibly to more effective prevention.